AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 13: Pulmonary Disease, Including Asthma

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, review of more than 15,000 leads about potential topics has resulted in identification and tracking of about 1,600 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 950 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the one topic in the system for which (1) preliminary phase III or later data were available; (2) information was compiled by September 21, 2012, in this priority area; *and* (3) we received six to nine sets of comments from experts between March 20, 2012, and October 26, 2012. (Thirty-eight topics in this priority area were being tracked in the system as of October 26, 2012.) For the Potential High-Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present one summary on a single topic (indicated below by an asterisk) that emerged as having potential for high impact on the basis of experts' comments. Readers are encouraged to read the detailed information on the intervention that follows the Executive Summary.

Priority Area 13: Pulmonary Disease, Including Asthma

Topic	High-Impact Potential
1. * Ivacaftor (Kalydeco, VX-770) for treatment of cystic fibrosis in patients with G551D-*CFTR* mutation	Moderately high

Discussion

Pulmonary disease is a priority area in which relatively few interventions have been identified as meeting criteria for tracking in the AHRQ Healthcare Horizon Scanning System. The experts deemed one topic as having potential for high impact—a new disease-modifying drug targeted at one of the genetic mutations seen in patients with cystic fibrosis (CF).

Ivacaftor (Kalydeco, VX-770) for Treatment of Cystic Fibrosis in Patients with G551D-*CFTR* Mutation

- **Key Facts**: Current therapies for CF have improved median survival times, but patients with CF still have a shorter-than-normal life expectancy and require extensive treatment over a lifetime to maintain their health as well as possible. Thus, an unmet need exists for novel, effective therapies to improve outcomes in this patient population. The oral tablet ivacaftor (Kalydeco™, VX-770, Vertex Pharmaceuticals, Inc., Cambridge, MA) targets the defective

CF transmembrane conductance regulator (CFTR) protein that causes CF. The drug is intended as a first-line treatment for patients with the G551D-*CFTR* mutation—about 4% of patients with CF. Ivacaftor tablets are indicated for oral administration, one 150 mg dose every 12 hours for patients 6 years of age and older. The drug is in several phase III clinical trials cosponsored by the Cystic Fibrosis Foundation (Bethesda, MD). In trials, effects on pulmonary function were reported as early as 2 weeks, and a statistically significant treatment effect was reported to be maintained through week 48. Also through week 48, investigators reported, patients given ivacaftor were 55% less likely to have a pulmonary exacerbation as patients given placebo. Ivacaftor in combination with another experimental CF drug, VX-809, has also been shown to improve lung function in patients with CF who have two copies of the *CFTR*-F508del mutation, according to recent phase II trial results. The F508del mutation occurs in about 70% of patients with CF, giving ivacaftor the potential for a much broader indication in the future. Additionally, ivacaftor is being evaluated in 10 other *CFTR* mutations known to cause CF, which could also expand the indicated patient population.

- On January 31, 2012, the U.S. Food and Drug Administration granted marketing approval for ivacaftor for treating patients aged 6 years and older who have a G551D mutation in the *CFTR* gene. Ivacaftor costs about $294,000 per year, and some financial analysts expect that third-party payers would cover it because other effective therapies for CF are lacking. Additionally, the manufacturer is expected to implement stratified pricing terms based on patient insurance status and income. Third-party payers have begun to develop policies; generally, payers are categorizing the drug as a specialty pharmaceutical requiring prior authorization for those who have prescription drug coverage. Copayments vary according to the terms of a patient's benefits.
- **Key Expert Comments**: Overall, experts commenting on this topic were moderately confident that this drug could meet the need for a novel, effective, oral treatment for CF, although this view was tempered by the fact that the drug is intended for only the 4% or so of patients with CF who have the mutation. Experts anticipated that this drug would affect current care processes and patient management by offering patients a convenient oral therapy to directly treat CF's cause, which could reduce the need for intravenous treatments, ventilation therapy, and chest physiotherapy, if the drug halts disease progression. The $294,000 annual cost of ivacaftor therapy was identified as a potentially controversial issue. Even for patients with prescription drug coverage, copayments are expected to be significant.
- **Potential for High Impact**: Moderately high

Pulmonary Disease, Including Asthma, Interventions

Ivacaftor (Kalydeco, VX-770) for Treatment of Cystic Fibrosis in Patients with G551D-*CFTR* Mutation

Current therapies for cystic fibrosis (CF) have improved predicted median survival, but patients with CF still have a shorter-than-normal life expectancy and require extensive treatment over a lifetime to maintain good health as much as possible. Thus, an unmet need exists for novel, effective medications to improve outcomes in this patient population. Ivacaftor (Kalydeco™, VX-770, Vertex Pharmaceuticals, Inc., Cambridge, MA) is a small-molecule, CF transmembrane conductance regulator (CFTR) modulator that improves the function of the *CFTR* gene by increasing CFTR activity in transporting negatively charged chloride ions across the cell membrane to the cell surface, improving hydration and clearing mucus in patients with CF.[1,2] Ivacaftor also promotes functional activity for two other *CFTR* mutations (i.e., F508del, R117H) and has some effect on the wild-type *CFTR* gene. Ivacaftor targets the defective protein that causes CF and is intended as a first-line treatment for the 4% of patients with CF who have the G551D mutation.[3] Ivacaftor is administered 150 mg twice daily with fat-containing food in patients 6 years of age and older.[4]

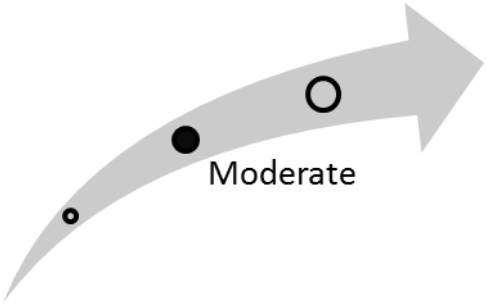
Ivacaftor is being investigated in several phase III clinical trials. In a randomized, double-blind, placebo-controlled, phase III clinical trial, cosponsored by the Cystic Fibrosis Foundation (Bethesda, MD) and the drug's manufacturer, patients (n=161) with at least one copy of CF mutation G551D given ivacaftor had a predicted forced expiratory volume in 1 second measurement that was 10.6 percentage points higher than patients treated with placebo through week 24 ($p<0.001$).[5] Effects on pulmonary function were observed as early as 2 weeks, and a significant treatment effect was maintained through week 48. Also through week 48, patients given ivacaftor were 55% less likely to have a pulmonary exacerbation than patients given placebo ($p<0.001$). Patients treated with ivacaftor also demonstrated a significant improvement in quality of life ($p<0.001$). By 48 weeks, patients treated with ivacaftor had gained significantly more weight and secreted significantly less chloride in sweat samples (a key indicator for *CFTR* activity; $p<0.001$ for both measures). The incidence of adverse events was similar with ivacaftor and placebo, with a lower proportion of serious adverse events with ivacaftor than with placebo (24% vs. 42%).[5] Ivacaftor in combination with another experimental CF drug, VX-809, has also been shown to improve lung function in patients with CF who have two copies of the *CFTR*-F508del mutation, according to recent, phase II trial results.[6] The F508del mutation is the most common CF mutation, occurring in about 70% of patients with CF.[7] Additionally, the manufacturer is sponsoring a study to evaluate the efficacy of ivacaftor in patients with CF caused by other known mutations including: R117H , G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D.[8,9] Thus, ivacaftor may gain a broader patient indication in the future.

On January 31, 2012, the U.S. Food and Drug Administration granted marketing approval for ivacaftor for treating patients aged 6 years and older who have a G551D mutation in the *CFTR* gene.[10] Ivacaftor's annual pricing was set at about $294,000.[11] The manufacturer has implemented stratified pricing terms based on patient insurance status and income.[12] While ivacaftor's annual price is high, pricing was purported to be derived following conversations with patients, physicians, and payers.[13] Third-party payers have begun to develop policies; generally, they are categorizing the drug as a specialty pharmaceutical requiring prior authorization for those who have prescription drug coverage. Copayments vary according to the terms of a patient's benefits.

Clinical Pathway at Point of This Intervention

Routine use of inhaled medications, ventilators, and/or chest physiotherapy helps to release the thick mucus associated with CF, which damages lung tissue over time. Patients with CF often require chronic use of inhaled, intravenous or oral antibiotics to prevent or treat acute infections in lungs already weakened by disease. Lung transplantation can reduce the effects of CF for some individuals.[14] As the disease progresses, some patients require mechanical breathing support, especially while sleeping. Ivacaftor is intended as a first-line treatment for patients with CF who have the G551D-*CFTR* mutation, and it can be used in conjunction with physiotherapy, mechanical devices, and antibiotics as needed.

Figure 1. Overall high-impact potential: ivacaftor (Kalydeco, VX-770) for treatment of cystic fibrosis in patients with G551D-*CFTR* mutation



Overall, experts commenting on this intervention expressed some confidence that this drug has potential to meet the need for a novel CF treatment that can improve health outcomes, although this view was tempered by the fact that CF is relatively rare and this drug is intended for only the approximate 4% of patients with CF who have this specific mutation. Because the drug is intended to be delivered orally, it could reduce the need for visits to health care facilities for regular oxygen, chest, and intravenous therapies. However, because of the small patient population and the drug's oral administration, ivacaftor is not expected to have a major impact on health care processes such as staffing or infrastructure requirements; thus, the experts expected it could be easily adopted. The $294,000 annual cost of ivacaftor therapy was identified as a potentially controversial issue. Forthcoming information regarding third-party payer coverage, patient copayments, real-world clinical efficacy, and offsets of other health care costs from improved outcomes from the drug will help to elucidate and better define these issues. Based on this input, our overall assessment is that this intervention is in the moderate potential high-impact range.

Results and Discussion of Comments

Six experts, with backgrounds in clinical practice, research, or health systems, offered perspectives on this intervention.[15-20] Experts generally agreed that the unmet need for novel treatments for CF is important, particularly if those treatments are disease-modifying instead of merely palliative. However, experts stated that the importance of this unmet need is tempered because CF is a rare condition and that within the small population affected by CF, 96% of patients would not be eligible for this treatment.

Based on positive clinical-trial results, ivacaftor appears to have a sound theory underlying its mechanism of action and potential to improve patient outcomes, the experts said. However, one health systems expert noted that additional clinical trials evaluating quality of life should be performed to better evaluate the drug's impact.

One expert representing a clinical perspective stated that the oral administration of ivacaftor could improve health disparities because rural patients and "working families" commonly have barriers to treatment when they must travel frequently to a care facility for intravenous therapy.

Experts anticipated that this drug would affect current care processes and patient management by offering patients a convenient oral therapy to directly treat CF's cause, which could reduce the need for intravenous fluids, ventilation therapy, and chest physiotherapy, if the drug halts disease progression. However, clinicians will need to spend some time initially to explain to patients the advantages and limitations of the new therapy and how it affects their care.

Because the drug is intended to be administered as an oral treatment and because of CF's rarity, experts providing comments did not think it would have a major impact on health care operations such as staffing and infrastructure needs. However, some experts suggested that if this drug is proven to be effective, it might reduce frequency of outpatient visits and inpatient care for flares and complications for patients with the affected mutation, requiring significantly less treatment resources.

The experts stated that the current price of the drug is quite high, but overall, the price may have limited impact because of the small number of patients eligible for this therapy. Additionally, reductions in oxygen and chest therapy, hospitalizations, and other complications could significantly offset costs in the long term. However, one expert representing a health systems perspective estimated that treating all eligible patients with ivacaftor would cost the health care system about $400 million annually, which the reviewer regarded as an unsustainable trend for a disease that affects such a small population of patients.

Although one clinical expert stated there will always be some patients hesitant about any new drug, the experts thought patient and clinical acceptance of ivacaftor would be wide and rapid. Possible barriers to acceptance include issues that could arise from coverage and costs such as high patient copayments. Additionally, if physicians observe limited efficacy in clinical practice they could be hesitant to prescribe such an expensive drug.

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